REMARKS

Claims 1, 3-17, 19-68, and 70 are currently pending in the application. Claim 1 is amended. Support for amended claim 1 can be found on page 10, lines 31-32. No new matter is added by this response.

Applicant wishes to than Examiner Gambel for the telephone interview of December 23, 2003 with Applicant's representatives. Applicant submits that the subject matter of that interview is incorporated into the following response.

Rejection of Claims 1, 5-9, and 15 Under 35 U.S.C. 102(e)

The Examiner has maintained the rejection of claims 1, 5-9 and 15 under 35 U.S.C. 102(e) as being anticipated by Maraskovsky et al. (U.S. Pat. No. 6,017,527). The Examiner asserts that the claims relate to methods of vaccinating a mammal to a selected antigen comprising administering a vaccine comprising a CD40 ligand-enhanced cell, wherein the CD40 ligand of the CD40 ligand enhanced cell is engineered; that is, comprises a heterologous cell membrane binding moiety. The Examiner rejects Applicants distinction of the claims over the teachings of Maraskovsky (that Maraskovsky does not teach a CD40 ligand-enhanced cell in which the CD40 ligand is engineered), asserting that Applicant's novelty argument is based only on the method of production of a claimed product. The Examiner asserts that all that is required of the claims is the "administration of a vaccine composition comprising a CD40 ligand-enhanced cell" and that the claims do not require the administration of an "engineered ligand for CD40". Applicant respectfully submits that the Examiner has misunderstood the claimed invention, and therefore Applicant's distinction over Maraskovsky et al. Accordingly, Applicant has amended claim 1 to clarify the invention, and to make more clear the distinction of the claimed invention over Maraskovsky.

Applicant submits that the claimed invention is a method of vaccinating a mammal to a selected antigen comprising administering a vaccine composition comprising a CD40 ligand-enhanced cell wherein the CD40 ligand-enhanced cell comprises the selected antigen and wherein the CD40 ligand enhancement of the CD40 ligand-enhanced cell is derived from the

admixture of the antigen bearing cell with a CD40 ligand comprising a heterologous cell membrane binding moiety. Support for amended claim 1 may be found on page 10, lines 30-31 of the specification. Thus, in contrast to the Examiner's assertion, the claimed invention **does** require the administration of an engineered ligand for CD40; that is **the CD40 ligand of the claimed CD40 ligand-enhanced cell is a ligand for CD40 which bears a heterologous cell membrane binding moiety**. This is not merely claiming the method of production of a product. Instead, the claims recite a property of the CD40 ligand-enhanced cell, namely, that the CD40 ligand is engineered, and thus comprises a heterologous cell membrane binding moiety.

The Examiner asserts that Maraskovsky teach methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. The Examiner notes that Maraskovsky also teaches transfection of dendritic cell to express the cytokines. Applicant submits that there is no teaching in Maraskovsky directed to a CD40 ligand which comprises a heterologous cell membrane binding moiety as required by the present claims. As noted by the Examiner, the burden is on the patent applicants to establish a patentable distinction between the claimed invention and the prior art. Applicant submits that they have done exactly that: the claims of the present invention require that the vaccine composition include a CD40 ligand comprising a heterologous cell membrane binding moiety, and this teaching is not found anywhere in Maraskovsky. Simply put, the claims expressly require that the CD40 ligand of the CD40 ligand enhanced cell be a ligand for CD40 which comprises a heterologous cell membrane binding moiety, and this requirement is not met by the teachings of Maraskovsky. Since the standard for anticipation of a claimed invention is that the prior art must teach each and every element of the claimed invention, either expressly or inherently, Maraskovsky cannot anticipate the claimed invention because it does not teach all the elements expressly recited in the claims.

Rejection of Claims 1 and 5-9 Under 35 U.S.C. 103(a)

The Examiner has rejected claims 1 and 5-9 under 35 U.S.C. §103(a) as being unpatentable over Maraskovsky et al. in view of Dullforce et al. (Nature Medicine, 4: 88, 1998), and/or Heath et al. (Eur. J. Immunol., 24: 1828, 1994), and/or Caux et al. (Research in

Immunology 145: 235, 1994). The Examiner asserts that Maraskovsky teach the methods of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. The Examiner notes that Maraskovsky does not teach the administration of agonistic CD40-specific antibodies per se. The Examiner asserts that each of Dullforce, Heath, and Caux teach anti CD40 antibodies which are capable of stimulating immune responses. The Examiner implies that it would have been obvious to one of skill in the art to combine the teachings of anti-CD40 antibodies as taught by Dullforce, Heath, and/or Caux with the "antigen" expressing activated dendritic cells as taught by Maraskovsky to arrive at the present invention. Applicants respectfully disagree.

For the reasons described below, the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. *Id.* The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The cited combination does not teach all the claim limitations

Applicant submits that combined teachings of the references cited by the Examiner do not result in the claimed invention. As discussed above, Maraskovsky teaches that activated dendritic cells which present processed antigen on their surface and which may be mixed with CD40 ligand, elicit an immune response. Maraskovsky does not teach a CD40 ligand which comprises a heterologous cell membrane binding moiety as required by the present claims. The deficiencies in the teachings of Maraskovsky are not remedied by the teachings provided by

Dullforce, Heath, or Caux. None of Dullforce, Heath, or Caux teach an engineered CD40 ligand, or any other engineered proteins; that is, none of the references teach a CD40 ligand which comprises a heterologous membrane binding domain. Thus, the combination of the teachings of Dullforce, Heath, or Caux with Maraskovsky does not result in a vaccine composition comprising a CD40 ligand enhanced cell comprising an antigen bearing cell admixed with an engineered CD40 ligand.

Accordingly, Applicant submits that the invention is non-obvious over the teachings of Maraskovsky in combination with one or more of Dullforce, Heath, or Caux. Applicant therefore requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 5-14, 17-18, 21-25, 28, 29, and 69 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 5-14, 17, 21-25, 28, and 29 under 35 U.S.C. §103(a) as being obvious over Maraskovsky, in view of Dullforce, Heath, and Caux, and in further view of McHugh et al. (PNAS, 92: 8059, 1995). Applicant respectfully disagrees.

Applicant has discussed previously the reasons why the present invention is not obvious over the teachings of Maraskovsky in view of Dullforce, Heath, and Caux. The Examiner is now adding the teachings of McHugh and the teachings of the present specification with respect to membrane attachment moieties to suggest that the claimed invention is obvious. Applicant submits that there is no motivation to make the combination suggested by the Examiner.

Maraskovsky teaches two primary embodiments for combining dendritic cells with a CD40 binding protein. In the first, the specification teaches that the dendritic cells, which express CD40 on their surface, are mixed with a CD40 binding protein in order to activate the dendritic cells to process antigen (col. 2, lines 1-2; 8-9). In the second embodiment, the specification teaches that the activated dendritic cells can be "administered to the individual prior to, concurrently with or subsequent to administration of cytokines that modulate an immune response, for example a CD40 binding protein **(i.e., soluble CD40L)**" (col. 2, lines 15-19; emphasis added). The specification further teaches that a particularly preferred cytokine is CD40 ligand, and that a "soluble form" has been described (col. 11, lines 59-60). Moreover, the other

cytokines and immunostimulatory molecules taught by Maraskovsky which can be administered along with an activated dendritic cell are soluble (see, e.g., col. 11, lines 50-60). Thus, Maraskovsky clearly teaches the **co-administration of a soluble cytokine and an activated dendritic cell**.

Applicant submits that McHugh teaches a construct comprising a GPI moiety fused to B7 molecules (also referred to as CD80), and the use of the fusion protein, incorporated into the membrane of tumor cells, to provide a costimulatory signal needed to stimulate T cells. Applicants submit that not only does McHugh not teach or even suggest the use of a GPI moiety linked to CD40 ligand (i.e., an engineered CD40 ligand), or the use of such an engineered CD40 ligand in a mixture with an antigen bearing cell for the purpose of vaccinating a mammal, but McHugh also acknowledges that the specific teachings relating to GPI-B7 are unpredictable. The Examiner asserts that one of skill in the art would have been motivated to create membrane linked anti-CD40 antibodies to mix with the activated dendritic cells of Maraskovsky, despite Maraskovsky's teaching that the cytokine should be **soluble**, and in view of the acknowledgment in McHugh that the GPI linked system may differ from system to system. The Examiner notes that McHugh does not teach CD40 ligand, but teaches that other co-stimulatory molecules are known in the art and that a candidate molecule can be quickly tested to determine "the proper combination need [sic] to create immunogenic cells that may be used in therapy", Applicant submits that this is insufficient motivation to make the combination suggested by the Examiner. Maraskovsky teaches that a co-stimulatory cytokine should be soluble, and does not teach or even suggest that membrane bound CD40 ligand would be desirable in a vaccine composition. Thus, one of skill in the art, given the teachings of Maraskovsky would not have been compelled to apply the membrane attachment teachings of McHugh. Likewise, McHugh does not teach linking CD40 to GPI, and moreover, teaches that the utility of GPI as a membrane anchor for co-stimulatory molecules may differ between systems. At best, this combination provides motivation to one of skill in the art to try out or experiment with various co-stimulatory preparations, but cannot be said to provide the motivation to make the **claimed invention**. In essence, the Examiner's argument is that, based on Maraskovsky's teaching of soluble CD40 ligand, and McHugh's teaching of limited stability of GPI linked B7, and unpredictability between different systems, combined with the knowledge in the art of myriad costimulatory

molecules one of skill in the art would be sufficiently motivated to select specifically from the genus of costimulatory molecules, CD40 ligand as a costimulatory molecule and modify specifically a CD40 ligand so as to contain a heterologous cell membrane binding domain (despite the fact that none of the references cited teach or suggest that membrane attachment of CD40 ligand is operable or even desirable), and to provide the engineered CD40 ligand in admixture with an antigen bearing cell to produce a vaccine composition. Applicant submits that this motivation is simply not present in the combination of references cited by the Examiner, and that the Examiner's rationale for rejection of the claims could best be classified as rejecting the claims as being obvious to try, which is not the legal standard for obviousness under 35 U.S.C. §103.

The Federal Circuit has long held that "obvious to try" does not constitute "obviousness." The court in *In re O'Farrell* (853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988)) made an excellent distinction between these two concepts. Judge Rich noted that "[a]ny invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?" (*Id.* at pages 1680-81). He went on to state that

> The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *[4 case cites omitted]*. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, at 1681). The prior art cited by the Examiner clearly falls into Judge Rich's second category. The combination of Maraskovsky and McHugh (with or without the other cited references) provides only general guidance, particularly in view of Maraskovsky's teachings that the CD40 ligand should be soluble and not membrane bound, and provides no more than motivation for one of skill in the art to explore a new technology, and does not render the claimed invention obvious.

In addition, McHugh teaches that the GPI moiety is to be coupled to the C-terminal end of a desired protein for incorporation into the cell membrane. Applicants submit, however that, as shown in Exhibit A (GenBank Accession No P29965; filed with Applicant's response of April 7, 2003), the C-terminus of the CD40 ligand is extracellular. That is, it is the C-terminus of the CD40 ligand which is likely to bind to CD40. Since, as taught by McHugh, GPI moieties link to the carboxy-terminus of proteins, one of skill in the art would expect that the attachment of a GPI moiety to the C-terminus of CD40 ligand would interfere with the binding of CD40 ligand to its receptor. Thus, one of skill in the art would not have been motivated, absent the teachings of the present invention, to modify a CD40 ligand by attaching a carboxy-terminal GPI moiety. Where the CD40 ligand is an antibody to CD40, Applicants submit that one of skill in the art would be likewise unmotivated to combine the teachings of Maraskovsky, Dullforce, Heath, and Caux, cumulatively relating to soluble CD40 binding proteins, with the GPI moieties taught by McHugh, because one of skill in the art would not be able to predict how the attachment of a GPI moiety to the C-terminus of a soluble anti-CD40 antibody would affect the ability of the antibody to bind CD40. In fact, as noted above, McHugh teaches that the immune response elicited by different molecules coupled to GPI may differ.

With respect to the Examiner's assertion that the required motivation to combine the teachings of the cited references is provided by the specification's disclosure that it was well known to engineer the attachment of a lipid to a molecule such as a peptide to permit the complex to be stably associated with a cell membrane, Applicant respectfully submits that the Examiner is in error. Applicant submits that it is well established law that the level of skill in the art (e.g., the technique for modifying a CD40 ligand to include a cell membrane binding moiety) cannot be relied upon to provide the suggestion to combine references (*Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999)). Thus, the mere fact that the technology existed to modify a protein to be incorporated into a cell membrane does not provide the level of motivation necessary to make the combination suggested by the Examiner.

Accordingly, Applicant submits that the invention is not obvious over the teachings of Maraskovsky alone or in combination with Dullforce, Heath, Caux, and/or McHugh because there are no teachings in these references, alone or taken together, to motivate one of skill in the

art to make the claimed invention. Applicant therefore requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 3, 4, and 70 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3, 4, and 70 under 35 U.S.C. § 103(a) as being obvious over the combination of Maraskovsky, Dullforce/Heath/Caux, and McHugh and further in view of Jacquier-Sarlin et al. (Immunology 84: 164, 1995).

The Examiner asserts that the previous combination differed from the claimed invention in that the prior combination did not teach the addition of the alpha chain of C3b. The Examiner asserts that Jacquier-Sarlin teaches the alpha chain of C3b. Applicant submits that, as described above, there is no motivation to combine the teachings of Maraskovsky, Dullforce, Heath, Caux, and/or McHugh, and further, that even if the references were combined (with respect to Maraskovsky, Dullforce, Heath, and Caux) the resulting combination would not teach the claimed invention. Applicant submits that the teachings of Jacquier-Sarlin do not remedy the deficiencies in the teachings of the other references, and therefore cannot be combined with the previously cited references to render the invention obvious. Jacquier-Sarlin merely teaches the ability of the complement fragment C3b to modulate antigen processing. Jacquier-Sarlin does not teach CD40 ligand, or a method of vaccinating an animal comprising administering a CD40 ligand enhanced cell which comprises an engineered ligand for CD40. Jacquier-Sarlin does not teach an engineered CD40 ligand, and does not provide teachings which would provide the motivation absent from the combination of the other cited references to combine the GPI moieties of McHugh with the co-stimulatory strategy of Maraskovsky.

Accordingly Applicant submits that the claims are non-obvious in view of Jacquier-Sarlin taken alone, or in combination with the other cited references. Applicants therefore request that the rejection be reconsidered and withdrawn.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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